

Physiology of the vascular system

The function of circulation is HEMOSTASIS

Functional parts of the circulation:

- 1- The aorta and large arteries transport blood under high pressure to the tissues i.e. forward flow.
These arteries are rich in elastic lamina. They are described as "elastic arteries".
They distend during ventricular ejection and recoil during ventricular diastole, maintaining blood flow and preventing marked changes of arterial pressure.
If arterial elasticity decreases, there is marked elevation of pressure during ventricular ejection and marked drop of pressure during diastole.
- 2- The small arteries and arterioles act as resistance vessels.
They have strong muscular wall that can close the arteriole completely or dilate it several-fold.
- 3- The capillaries are exchange vessels, between the blood and interstitial fluid (ISF).
- 4- Veins transport blood from the venules back to the heart, and they serve as a major reservoir of extra blood.
Veins are capacitance (compliance) vessels.
- 5- The lymphatic vessels can carry proteins and large particles away from the tissue spaces.

Vascular endothelium:

Despite its microscopic thickness ($< 1\mu\text{m}$), the endothelium is a large organ and has many functions.

The endothelium responds to:

- 1- Stretch.
- 2- Blood flow.
- 3- Circulating substances.

The response of the endothelium to these stimuli involves secretion of:

- 1- Growth factors that regulate vascular growth and remodeling.
- 2- Vasoactive substances that regulate vascular tone.

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In addition, the endothelium is involved in the regulation of homeostasis and immune reactions:

<u>Vasodilators:</u> - Nitric acid (NO) - Prostacyclin (PGI ₂)	<u>Vasoconstrictors:</u> - Endothelin -1 (ET-1) - Angiotensin II
<u>Antithrombotic:</u> - Tissue plasminogen activator (TPA). - Prostacyclin (PGI ₂)	<u>Prothrombotic:</u> - Plasminogen activator inhibitor -1 (PAI-1) - Thromboxane A ₂
<u>Growth inhibitors:</u> - Nitric acid (NO) - Transforming growth factor- β	<u>Growth stimulators:</u> - Vascular endothelial growth factor - Angiotensin II
<u>Anti-inflammatory:</u> - nitric acid (NO)	<u>Pro-inflammatory:</u> - Tumor necrosis factor- α

Volumes of blood in different parts of the circulation:

84 % of blood volume is in the systemic circulation, 64% in the veins, 13% in the arteries, and 7% in the arterioles and capillaries. The remaining 16% of the blood is in the heart and lungs (heart contains 7% and the pulmonary vessels 9%).

Pressure in the various portions of the circulation:

- The arterial pressure in the aorta 120 mmHg (systolic) and 80 mmHg (diastolic) with mean pressure 90 mmHg.
- The pressure in the systemic capillaries 35 mmHg at the arteriolar end & 15 mmHg at the venous end, with an average "functional" capillary pressure of 25 mmHg.
- The pulmonary arterial pressure 25 mmHg systolic and 8 mmHg diastolic with a mean pulmonary arterial pressure of 16 mmHg. The mean pulmonary capillary pressure is only 10 mmHg. This low value is important to prevent pulmonary edema.

Biophysical considerations:

Mechanical forces acting on blood vessel wall:

The pumping action of the heart is a force which is manifested on the vessel wall in three forms:

1- Pressure:

Pressure is the perpendicular force per unit area applied on a surface of vessels.

Blood pressure can be regarded as compressive stress acting on vessel wall. However, in medical practice pressure is commonly measured in mmHg. One mmHg = 0.133 kilo Pascal (KPa), Pascal is Newton/m².

2- Tension:

Tensile force (measured in Newton) acts parallel to the surface of the vessel and tends to stretch vessel wall.

3- Shear stress:

It is the tangential drag force produced by blood moving across the endothelial surface.

Normally, 20-40 dyne/cm² in large arteries
Changes in shear stress produce, on long run, marked changes in the expression of genes in the endothelial cells.

Blood flow

Definition:

Volume of blood that crosses a point per unit time (e.g., cm³/second) is the cardiac output.

Relationship between flow (F), pressure (P), and resistance (R) in blood vessels:

$$A) \text{ Flow (F)} = \frac{\text{Pressure gradient } (\Delta P)}{\text{Resistance (R)}}$$

Resistance to blood flow is determined by:

- 1- Radius of the vessel (r): $R \propto 1/r^4$
- 2- Length of the vessel (L): $R \propto L$
- 3- Viscosity of blood (η): $R \propto \eta$

i.e.

$$B) R \propto \frac{L \eta}{r^4}$$

Poiseuille- Hagen formula:

From equations 1 & 2

$$F = \pi \Delta P r^4 / 8 \eta L$$

Radius and Resistance:

If the radius of a vessel is increased by only 20 %
Resistance is reduced to 50 % of its previous value.

While flow through a vessel is almost doubled

Viscosity and Resistance:

Significant increases in viscosity are observed when:

- 1- Plasma proteins e.g. immunoglobulins are markedly elevated.
- 2- Red cells are abnormally rigid as in hereditary spherocytosis

Blood flow is most commonly measured using "Ultrasonic Doppler Flow Meter"

Calculation of total peripheral resistance (TPR) in systemic circulation:

Total blood flow in cardiovascular system is the cardiac output (COP).

This flow occurs under the effect of a pressure gradient between aortic pressure (mean arterial pressure MAP) and right atrial pressure RAP).

$$COP = (MAP - RAP) / TPR$$

$$TPR = (MAP - RAP) / CO$$
$$= (90 - 0) / 5$$

Therefore, TPR is about 18mmHg/L/min

Calculation of the resistance in the pulmonary circulation (Pul R):

Total blood flow in pulmonary circulation is the cardiac output (COP).

This flow occurs under the effect of a pressure gradient between pulmonary pressure (mean pulmonary pressure MPP) and left atrial pressure LAP).

$$PulR = (MPP - LAP) / COP$$
$$= (15 - 8) / 5$$

Therefore, pulmonary vascular resistance is about 1.4 mmHg/L/min.

Velocity of blood flow and vascular cross-sectional area:

The velocity of blood is inversely proportional to vascular cross-sectional area.

Cross sectional area of the various vascular segments:

Vessel	Cross-sectional area (cm ²)	Velocity of blood
Aorta	2.5	0.5 meter/sec
Small arteries	20	
Arterioles	40	
Capillaries	2500	0.5 mm /sec
Venules	250	
Small veins	80	
Vena cava	8	

Laminar (Streamline) flow:

Within the blood vessels, blood flows in layers.

The layer in contact with the wall is almost stationary.

The velocity of flow of the next layer is higher.

Maximum velocity of flow occurs at the center of the vessel.

Flow continues to be laminar up to a certain velocity. As blood flow velocity exceeds this critical value, flow becomes turbulent.

Laminar flow is silent, but turbulent flow creates sounds (murmurs).

Turbulence is related to:

The velocity of the blood, the viscosity of the blood, and the diameter of the vessel

Constrictions of an artery increase the velocity of the blood flow through the constriction, producing turbulence, and consequently sound e.g. Korotkoff sounds during measurement of blood pressure.

Turbulence occurs more frequently in anemia because the viscosity of the blood is low and the velocity of blood is high.

Critical closing pressure:

Tissues exert pressure on blood vessels.

If the pressure inside the vessel is less than tissue pressure the vessel collapses and blood flow stops.

The vessel pressure below which the vessel is closed and blood flow stops is known as the critical closing pressure.

It is about 15mmHg.

Systemic arterial compliance:

Compliance is a ratio $\Delta V / \Delta P$ or volume change for unit pressure.

- Total systemic arterial compliance is mainly determined by the aorta and its major branches

- When arterial compliance decreases (e.g. in atherosclerosis), arterial pressure changes are higher for the same volume pumped during ventricular ejection.

- Arterial compliance serves two functions:

- 1- Converts intermittent flow in the aorta to continuous flow in peripheral vessels. Recoil of the arteries during diastole keeps pushing blood forwards when ventricles are relaxing.

- 2- Reduces work done by the heart. Cardiac work is defined as Pressure X volume

Therefore, for a given volume (cardiac output), when compliance is low the pressure is high and the work increases.

Resistance and compliance vessels:

- Small arteries and arterioles are the principle site of peripheral resistance.
- * - Capacitance vessels are the veins that are partially collapsed. They can receive large amount of blood without marked change in pressure (blood reservoir).

Law of Laplace

The wall tension in thin-walled cylinder (T) e.g. blood vessels, equals the product of the transmural pressure (P) and the radius of the vessel (r).

$$T = Pr$$

$$\text{Or, } P = T/r$$

Since the tissue pressure in the body is low, P equals the pressure inside the vessel.

1- In a thin-walled asymmetric viscus:

$$P = T (1/r_1 + 1/r_2),$$

Where r_1 and r_2 are the two principle radii of the viscus

In a sphere (symmetric): $r_1 = r_2$

$$\text{So } P = 2 T / r$$

2- In a cylinder as blood vessel, one radius is infinite ($1 / \infty = \text{zero}$):

$$P = T / r$$

- Consequently, the smaller the radius the lower the tension in the wall necessary to balance the distending pressure.
- Accordingly, the thin-walled structures as capillaries can withstand high pressure, since the developed wall tension will be small.

3- For a thick-walled structure e.g. left ventricle, a more appropriate form of the equation would be:

$$S = Pr / 2 w$$

Where S is the wall stress and w is wall thickness.

- Wall stress (S) is related to tension (T) and wall thickness (w) as follows:

$$T = S w$$

Arterial blood pressure

1- Definitions

2- Factors that determine the ABP

3- Physiologic variation in ABP

4- Regulation of ABP (Refer to page)

Definitions:

ABP:

Pressure of blood on wall of aorta & large arteries

Systolic blood pressure (SBP):

It is the peak pressure reached during systole.

It is about 120mmHg (normal range is 90 – 140 mmHg) in adults.

Diastolic blood pressure (DBP):

It is the lowest pressure during diastole and is about 80 mmHg (normal range is 60-90 mmHg) in adults.

Mean arterial pressure (MAP):

It is the average pressure throughout the cardiac cycle.

Mean arterial pressure = Diastolic pressure + $1/3$ pulse pressure = 90 mmHg

Mean arterial pressure is nearer to diastolic pressure i.e. lower than arithmetic mean because systole is shorter than diastole. However, when heart rate is rapid shortening affects diastole more than systole, so the mean arterial pressure becomes nearer to the true arithmetic mean.

Pulse pressure:

It is the difference between the systolic and diastolic pressure.

It is normally about 30- 50 mmHg

It is the cause of arterial pulse

Factors that determine the mean arterial blood pressure:

$$\text{Mean arterial pressure (MAP)} = \text{COP} \times \text{TPR} \\ = \text{SV} \times \text{HR} \times \text{TPR}$$

Accordingly, ABP is increased by: ++ SV, HR or TPR

1- Stroke volume:

++ SV increases the systolic more than the diastolic pressure.

Therefore the pulse pressure is increased.

2- Heart rate:

++ HR increases the diastolic pressure more than the systolic because less time is available for drop of pressure as the diastole is shortened.

The pulse pressure is decreased.

3- Total peripheral resistance:

++ TPR increases the diastolic more than the systolic pressure, therefore the pulse pressure decreases.

4- Arterial compliance:

-- Arterial compliance leads to atherosclerosis.

a- ++ systolic pressure because arteries are not able to distend enough to accommodate the stroke volume.

b- -- diastolic pressure because the ability of the arteries to recoil in diastole is decreased.

Pulse pressure therefore increases.

Physiological variations in ABP:

1- Age: ABP generally increased with age.

Normal ABP in infants is about 120/80 mmHg.

In children, about 100/65 mmHg

In young adults: about 120/80 mmHg.

In old age, it should not rise above 140/90 mmHg.

2- Sex: below the age of menopause, women usually have lower ABP than men of the same age.

However, after menopause ABP rises in women due to hormonal changes that occur after menopause.

3- Race: some races have higher ABP and higher incidence of hypertension than other races.

4- Circadian rhythm and ABP: in normal persons (working at daytime), ABP reaches peak value early in the morning and decreases to its lowest level at midnight.

These variations in ABP may amount to 15-25 mmHg. ABP changes follow sympathetic nervous system activity, which is minimal during nocturnal sleep.

5- Emotions: strong emotional stress elevates ABP.

6- Muscular exercise: changes in ABP during exercise depend on the type of muscle contraction.

a- if the contraction is isotonic, systolic pressure is moderately increased while diastolic pressure either falls or not changes.

b- If exercise involves isometric muscle contraction then both systolic and diastolic pressure are increased.

7- Respiration: ABP fluctuates with respiratory cycles (Traube-Hering waves). At the beginning of inspiration, blood pressure decreases because inflation of the lungs causes reflex vasodilatation. Pressure starts to rise and reaches maximum late in inspiration and at the beginning of expiration.

8- Effect of gravity on ABP:

In standing position, pressure in arteries below the level of left ventricle increases by 0.77 mmHg for each 1 cm below the level of the ventricles & vice versa.

The effect of gravity is abolished in lying position.

Capillary circulation

Capillaries contain 5-7 % of the circulating blood.

Structure of the capillary related structures:

- Metarterioles:

They are the terminal divisions of arterioles.

They have smaller muscle wall.

They terminate into true capillaries.

- Sometimes, the metarteriole is connected directly with the venule by a preferential channel (thoroughfare vessel).

- Precapillary sphincters:

They have little smooth muscle cells.

They surround the openings of the true capillaries.

- Met-arterioles and precapillary sphincters receive sympathetic innervation & respond to vasoactive substances,

- Capillary wall:

It is very thin (about one μm thick) being made up of a single layer of endothelial cells resting on a basement membrane.

The structure of the capillary wall varies from organ to organ depending on their functions.

Three types of capillary walls:

Capillary wall	Endothelial cells	Permeability	e.g.
1- Continuous	Tight junction	Low	CNS, muscles, lungs, adipose tissue
2- Fenestrated	Pores (fenestra)	Moderate	Kidney & intestine
3- Discontinuous	Large gaps	High	Liver & spleen.

- Pericytes:

Some capillaries have pericytes outside the endothelial cells.

These cells are characterized by:

- a- They have long processes that surround the vessels.
- b- They are contractile and release a wide variety of vasoactive agents.
- c- They regulate the flow through the junctions between endothelial cells.

Capillary pressure:

- The capillary pressure in human nail bed capillaries equals 25 mmHg at the arterial end, and 15 mmHg at the venous end.

However, capillary pressure is not the same in different parts of the body.

- Although capillary wall is very thin, yet it can withstand high pressure.

This is explained by LAPLACE LAW.

- The capillary wall becomes abnormally fragile (i.e. easily ruptures when pressure rises) in the following conditions:

- a- Old age
- b- Some allergic conditions.
- c- Ascorbic acid deficiency (scurvy) because of failure of the endothelial cells to be cemented together.

Capillary blood flow:

The capillary blood flow is:

1- Very slow (about 0.5 mm/s due to large total cross sectional area) to give enough time for exchange of materials between blood and interstitial fluid.

2- Intermittent, this is due to vasomotion.

Vasomotion is alternating contraction and relaxation of the metarterioles and precapillary sphincters.

a- During rest, they contract by sympathetic discharge which cause most capillaries to close & blood passes in thoroughfare vessels & metabolites accumulates.

b- Metabolites ++ CO₂, -- O₂, lactic acids & K⁺

→ relax of metarterioles & precapillary sphincters

→ ++ capillary flow which washes metabolites & so on.

This alternating opening and closure of capillaries occurs at a rate of 6-12 times per minute.

- In active tissues: concentration of metabolites increases. This leads to opening of larger number of capillaries. Vasomotion cycles occur more rapidly too.

Equilibrium with interstitial fluid:

The main function of capillaries is to exchange materials with interstitial fluid.

→ Three mechanisms are involved in this exchange:

1-Diffusion:

This is quantitatively the most important mechanism for exchange of materials across the capillary wall.

The rate of diffusion of substances across the capillaries depends on:

A) Factors related to Capillary permeability:

Discuss table page 10

Capillary permeability can change under different conditions (e.g.) during inflammation permeability increases.

B) Factors related to substance:

$$R \propto \frac{CAT}{MDM}$$

a- Concentration gradient:

Diffusion $\propto C_1 - C_2$

b- Lipid solubility:

Lipid soluble substances can diffuse through either cell membrane through pores and gaps between these cells.

The more the solubility the more will be rate of diffusion.

c- Molecular size:

This is important for (water-soluble) substances. →

The smaller the molecular size, the more will be their diffusion.

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Cell membrane
Pores

2- Trans- Capillary Filtration (Bulk flow): "Starling Forces":

This process depends on the balance of hydrostatic pressure gradient and osmotic pressure gradient:

a- Forces tending to move fluid outwards from capillaries into interstitial space:

a- Capillary hydrostatic pressure P_c (main force)

b- Interstitial colloid osmotic pressure (π_i)

Forces tending to move fluid inwards from interstitial space into capillaries:

- a- Interstitial hydrostatic pressure (P_i), and
- b- Capillary colloid osmotic pressure π_c (main force)

$$\text{Fluid movement} = k [(P_c + \pi_i) - (P_i + \pi_c)]$$

- The interstitial colloid osmotic pressure (π_i) is usually very small and can be ignored.
- The capillary filtration coefficient (k) is proportional to the permeability of the capillary wall and the area available for filtration.

Along a muscle capillary, the net force is as following:

- * At arteriolar end: $(37 + 0) - (1 + 25) = 11 \text{ mmHg}$
i.e. Fluid moves out from capillary into the interstitial space by a force of 11 mmHg
- * At venular end: $(17 + 0) - (1 + 25) = -9 \text{ mmHg}$
i.e. Fluid moves into the capillary by a force of 9 mmHg.

- The balance of Starling forces is different in other capillaries.

Fluid moves out along the entire length of the capillaries in the renal glomeruli.

While fluid moves in along the entire length of the capillaries in the intestine and lungs.

- It has been estimated that about 24 L of fluid are filtered through the capillaries per day (0.3 % of COP).

About 85 % of the filtered fluid is reabsorbed at the venous end of the capillaries.

The remainder returns to the circulation via the lymphatics.

3- Vesicular transport:

By this transport mechanism large lipid-insoluble molecules e.g., proteins, are transported across endothelial cells.

These molecules are engulfed by the endothelial cells at the vascular border by pinocytosis to be released at the interstitial border by exocytosis.

This mechanism provides tissues with molecules of high MW e.g. antibodies, cytokines and protein-bound hormones.

$$\begin{array}{r} 53.4 \\ 10 \\ \hline 53.5 \\ 2 \\ \hline 55.5 \\ 2.5 \\ \hline 58 \\ 5 \\ \hline = 5 - \end{array}$$

(89)

12

$$\begin{array}{r} 8 \\ 7 \\ \hline 15 \\ 2.5 \\ \hline 17.5 \end{array}$$

$$\begin{array}{r} 2 \\ 5 \\ 28 \\ \hline 35 \end{array}$$

(53.5)

$$\begin{array}{r} 7 \\ 69 \\ \hline 2 \\ 5.5 \\ \hline 72.5 \end{array}$$

The Reactions of capillaries to mechanical stimuli:

A) White reaction (line):

When a pointed object is drawn lightly over the skin, capillaries empty due to contraction of the precapillary sphincters in response to the mechanical stimulus.

B) Triple response:

When the skin is stroked firmly with pointed instruments; three things occur:

① Reddening at the site of injury appears in 10 seconds (red reaction). This is due to capillary dilatation as a direct response to pressure.

This followed in a few by:

② Local swelling (wheal) and around the injury is due to increased permeability of the capillaries and post-capillary venules in response to local vasodilators such as histamine, bradykinin and substance P.

③ Diffuse spreading (flare) around the injury caused by dilatation due to antidromic impulses.

vessels

Angiogenesis:

It is the process of developing new vessels by the migration and proliferation of the endothelial cells.

- It is the main form of new blood vessel formation in adults.

- In response to ischemia (inadequate blood supply), the vascular endothelial growth factor (VEGF) stimulates angiogenesis.

Lymphatic circulation

- The normal lymph flow is 2-4 L/day.

- Wall of the initial lymphatics in regions like the intestines and skeletal muscles has loose junctions between the endothelial cells.

The extra fluid enters through these loose junctions.

- Drainage of lymph is helped by the following mechanisms:

④ 1- The peristaltic contraction of the smooth muscles of the collecting lymphatics is the main factor pushing the lymph centrally.

⑤ Valves allow lymph to flow in only one direction (centrally).

③ 2- Contraction of skeletal muscles surrounding lymphatics squeezes lymph centrally.

① 3- Negative intra-thoracic pressure sucks lymph upwards.

② 4- Pulsations of the neighboring arterioles.

ao.
vessel
except
heart
suck lymph

- suck of heart
- thoracic pressure
- Arterial cont.
- venous cont.
- sympathetic

- Functions of lymphatics:

- 1- Drainage of the excess filtered fluid from capillaries not drained at the venous end of the capillaries.
- 2- The lymphatics can carry proteins and large particles away from the tissue spaces. An amount equal to 25% of total plasma proteins is returned by lymphatics to the blood each day.
- 3- Transport of absorbed long chain fatty acids and cholesterol from the intestine.
- 4- Removal of bacteria and their delivery to lymph nodes.

Interstitial Fluid (ISF) Volume

Factors that determine the ISF volume:

→ Capillary factors:

- ① { 1- The capillary hydrostatic pressure.
- 2- Capillary osmotic pressure.
- 3- The capillary filtration coefficient.
- 4- The number of active capillaries.
- 5- The ratio of pre-capillary to post-capillary venular resistance.

The pre-capillary constriction lowers the filtration pressure while the post-capillary constriction elevates it.

→ Other factors:

- ① { 1- The ISF pressure.
- 2- The lymph flow.
- 3- The total extra-cellular (ECF) volume.

Edema

Edema is abnormal large accumulation of ISF.

Because of the effect of gravity, the ISF tends to accumulate in dependent parts as lower limbs in the standing position, and back in the recumbent position.

Causes of increased ISF volume and edema:

1- Increased filtration pressure:

- a) Arteriolar dilatation.
- b) Venular constriction.
- c) Increased venous pressure (effect of gravity, increased total ECF volume, incompetent venous valves, venous obstruction and heart failure).

2- Decreased Osmotic Pressure Gradient Across Capillary:

- Decreased plasma protein level e.g.

- a) Nutritional edema.
- b) Liver cirrhosis (leading to decreased plasma proteins synthesis).

- (c) Kidney diseases as nephrosis (leading to loss of plasma proteins in urine).
- Accumulation of osmotically active substances in IS space.

3- Increased Capillary Permeability by:

(a) Substance P

(b) Histamine

(c) Kinins

e.g. in inflammation or burns

4- Lymphatic obstruction

It is caused by:

(a) Long standing diseases as elephantiasis

The edema fluid has high protein content with inflammations & fibrosis (non-pitting edema).

(b) Cancer cells.

(c) Surgical removal of lymphatic e.g. cancer breast.

Venous Circulation

Functions of veins:

1- Transport vessels:

Veins are transport vessels that offer little resistance to blood flow from tissues to the heart

2- Blood reservoir (capacity vessels):

Significant volumes of blood can be added to or removed from veins with only little changes in venous pressure 200 ml/mmHg.

Venous pressure:

Central venous pressure (CVP) "Right atrial pressure"

- Normal: 0.2 mmHg.

- Significance:

- (1) It is the main force for ventricular filling.
- (2) Difference between mean systemic filling pressure & CVP is the gradient for venous return.
- (3) It is an index of blood volume.
- (4) CVP is decreased in hemorrhage.
- (5) CVP is increased in right-sided heart failure.

Effect of gravity on venous pressure:

In the upright position, the pressure in peripheral veins changes in the following way:

- (1) Below the level of the right atrium, pressure increases by 0.77 mmHg for each cm below the level of the right atrium & vice versa.

Therefore, pressure in leg veins increases from 20 mmHg in recumbent position to about 80 mmHg during standing.

This may cause edema and varicose veins.

② On the contrary, the neck veins are collapsed. However, the dural sinuses have rigid walls and can not collapse.

Pressure in the dural sinuses is sub-atmospheric in standing (or) sitting position.

If one of the dural sinuses is opened (as in neuro-surgical operations) while the patient is seated, the sinus sucks air causing fatal air embolism.

③ The hydrostatic indifferent point (HIP):

Definition: transitional zone in which venous pressure remains constant in spite of changing body position.

Venous pressure at this zone is not affected by gravity.

Site: The HIP is located 5-7 cm below the level of the diaphragm.

Normally pressure at the HIP is about 10-11 mmHg.

The position of HIP is related to the capacity of both the thoracic and the lower limb veins.

e.g. if the capacity of the lower limb veins decreases, the HIP shifts upwards.

Since the right atrium lies above the HIP, then CVP decreases on standing.

This leads to decreased cardiac output and drop of arterial blood pressure.

This is called orthostatic hypotension.

During swimming, lower part of the body is immersed in water and the capacity of lower limb veins decreases. This shifts the HIP upwards nearly to the level of the heart.

Therefore, CVP is not decreased and consequently orthostatic hypotension does not occur during swimming.

Venous blood flow:

It is slower than arterial flow (about 25% of blood flow velocity in aorta).

The following integrated mechanisms help blood moving upwards towards the heart:

1- Thoracic Pump:

During inspiration, VR is increased due to:

- The intra-thoracic pressure falls from -4 mmHg to -8 mmHg.
- The intra-abdominal pressure increases from 5 to 6 mmHg.
- The gradient between abdominal and thoracic veins is increased. It equals $6 - (-8) = 14 \text{ mmHg}$. This helps venous return towards the heart.
- During expiration the pressure gradient equals $5 - (-4) = 9 \text{ mmHg}$. Thus, venous return is decreased during expiration.



2- Heartbeat Effects:

⊖ Atrial suction:

During rapid ejection phase, the atrioventricular (AV) ring is pulled down. This leads to sharp drop of atrial pressure with subsequent sucking of the blood from the great veins into atria.

⊖ Ventricular sucking:

During rapid filling phase, opening of tricuspid valve allow the low ventricular pressure to suck blood from atria.

3- Sympathetic venoconstrictor which occurs upon standing position.

4- Muscle pump:

The contraction of muscles during activity compresses the veins of the limbs.

5- Arterial pulsations are conducted to near by veins.

6- The venous valves:

The intima of the limb veins is folded to form venous valves.

Venous valves allow flow of blood only towards the heart.

If the valves are incompetent → varicose veins in lower limbs

Basic mechanisms of circulatory control

The aim of the circulatory control is to:

- 1- Increase the blood flow to active tissues.
- 2- Maintain the blood flow to the heart and brain in case of sudden changes such as hemorrhage.
- 3- Increase or decrease heat loss from the body by redistribution the blood between skin vessels and vessels in deeper tissues.

The circulatory adjustments occur by changes in:

- 1- Cardiac output.
- 2- Amount of blood pooled in or out from capacitance vessels (veins)
- 3- Diameter of the resistance vessels (arterioles).

Regulation of the diameter of arterioles

The diameter of arterioles is adjusted by:

- 1- Local vascular regulatory mechanisms (autoregulation).
- 2- Substances secreted by the endothelium.
- 3- Circulating vasoactive substances (*systemic regulation*).
- 4- Nerves that innervate arterioles.

1 & 2 are concerned more with regulation of blood flow locally in particular tissues.

3 & 4 are concerned more with systemic regulatory responses such as regulation of arterial blood pressure and redistribution of blood all over the body in such conditions as muscular exercise or in case of hemorrhage.

I- Autoregulation

Autoregulation means the intrinsic capacity of vascular beds to compensate for moderate changes in perfusion pressure by changing vascular resistance so that blood flow remains constant.

It is well developed in the kidneys.

Autoregulation depends on myogenic and / or metabolic mechanisms.

A) Myogenic autoregulation:

Aim

To maintain constant blood flow to an organ in spite of an INCREASE in its perfusion pressure

Mechanism:

As the pressure in the blood vessels rises, blood vessels are distended by the high pressure & vascular smooth muscle cells (VSMCs) are stretched. Stretch stimulates Ca^{+2} entry which causes contraction of VSMCs leading to vasoconstriction of the vessel.

Resistance is increased in face of the high pressure.

Thus, flow returns nearly to its initial value.

B) Metabolic autoregulation:

Aim

To maintain constant blood flow to an organ in spite of DECREASE in its perfusion pressure

Mechanism:

When perfusion decreases, the decreased flow causes vasodilator metabolites to accumulate and cause relaxation of the arterioles and precapillary sphincters.

This decreases the resistance and leads to increasing blood flow.

Vasodilator metabolites include

- Decreases in O_2 tension (hypoxia).
- Increased H^+ concentration (low pH, acidosis) by acidic metabolites e.g. lactic acid.
- Increased CO_2 tension (hypercapnia).

- Increased osmolarity (hypertonicity). *
- Rise in body temperature. •
- Accumulation of K^+ ions especially in skeletal muscles. *
- Adenosine in cardiac muscle. *
- Histamine in injured & inflamed tissues. •

Notes:

Active hyperemia:

This is the increases blood flow to active tissues caused by increased vasodilator metabolites.

Reactive hyperemia:

It is the increase in blood flow to a region when its circulation is re-established after a period of occlusion.

Arterioles distal to the occlusion dilate due to hypoxia and accumulation of vasodilator metabolites.

When the circulation is reestablished, blood flowing into the dilated vessels is increased.

This makes the limb feels warm and the skin burning red.

II) Substances secreted by the Endothelium

A) Nitric Oxide (NO):

- Formation:

NO is produced by the action of endothelial nitric oxide synthase (eNOS) enzyme on L-arginine in the endothelial cells.

- Stimuli that activate eNOS and increase NO production:

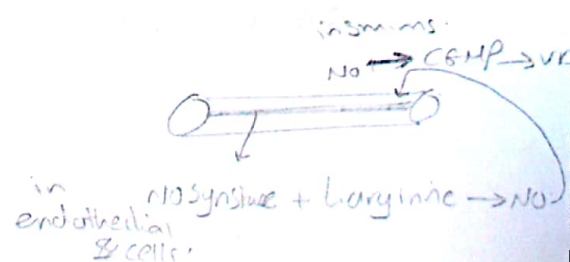
- 1- Acetylcholine.
- 2- Bradykinin.
- 3- Shear stress.

- NO acts on vascular smooth muscle cells (paracrine action) by activating guanylate cyclase enzyme. The result is increasing intracellular cyclic guanosine monophosphate (cGMP) which causes vaso-relaxation.

- Importance:

- 1- NO is important in the regulation of coronary, cerebral and pulmonary circulations. ③
- 2- NO is responsible for VD of penile arterioles leading to erection of penis. ②
- 3- The continuous release of NO is necessary for the maintenance of normal ABP. ①

NO production is reduced in patients with hypertension.



B) Endothelin-1:

- Three types of endothelins are formed in the human body: endothelin-1, endothelin-2 and endothelin-3.

Endothelin-1 is the primary type produced by endothelial cells.

It is the most potent vasoconstrictor agent yet known.

Endothelin-2 is found in kidneys and intestine.

Endothelin-3 is mainly found in brain.

- Endothelin receptors:

1- Endothelin receptor-A (ET_A) specific for endothelin-1.

2- Endothelin receptor-B (ET_B) that can bind the three endothelins.

- Cardiovascular actions of endothelin-1:

1- Vasoconstriction: Endothelin-1 acts via its ET_A receptors which are present on (VSMCs) results in Ca^{+2} influx that reduces VSMC contraction causing vasoconstriction.

2- Veins are more constricted by endothelins than arterioles.

3- Positive inotropic and chronotropic effect.

4- Strong coronary vasoconstriction.

5- Renal vasoconstriction and decreased glomerular filtration rate.

6- Increases the secretion of atrial natriuretic peptides, rennin, aldosterone and catecholamines.

7- Pulmonary broncho-constriction.

8- Release of nitric oxide from endothelial cells. This is mediated by ET_B receptor present on endothelial cells.

Vasodilator effect of released nitric oxide modulates the vasoconstrictor effect of Endothelin.

- Endothelin-1 secretion is increased by:

- a- Angiotensin II
- b- Catecholamines
- c- Vasopressin.
- d- Hypoxia
- e- Shear stress
- f- Thrombin

- Endothelin-1 secretion is decreased by:

- a- NO
- b- Prostacyclin
- c- Atrial natriuretic peptide

* CV actions of endothelin-1:

- 1- $ET_A \rightarrow VC$
- 2- $ET_B \rightarrow NO$

- 3- Veins more c than Arteries
- 4- Coronary constriction
- 5- +ve inotropic & chronotropic
- 6- Pulmonary constriction
- 7- renal constriction $\rightarrow$ $\downarrow$ reabs
- 8- Release of ANP

C) Prostacyclin:

- Prostacyclin is formed in endothelial from arachidonic acid.

- Its physiological functions include:

- ① a- Vasodilatation.
- ② b- Inhibition of platelets aggregation.
- ③ - Prostacyclin action is related to NO.

Prostacyclin facilitates NO release from endothelial cells.

In turn, NO potentiates Prostacyclin effect on smooth muscles.

III) Systemic Regulation by Hormones

A) Vasoconstrictor hormones:

- 1- Vasopressin (Antidiuretic hormone).
- 2- Epinephrine
- 3- Norepinephrine
- 4- Angiotensin II.

B) Vasodilator hormones:

- 1- Kinins
- 2- Natriuretic peptide.

Vasopressin (Antidiuretic hormone ADH):

- Secretion: - receptors

Vasopressin is synthesized in hypothalamus.

- It is stores in:

Posterior pituitary gland

- Stimuli increase vasopressin release from the posterior pituitary:

- ① Increased osmolarity of extracellular fluid by 1 %.
- ② Hypovolemia (loss of 10 % of blood): as in hemorrhage, dehydration and hypotension.
- ③ Angiotensin II.

- Actions:

1- The main function of vasopressin is to decrease water excretion by the kidney (hence the name antidiuretic hormone). This action is mediated via V_2 receptor.

2- Vasopressin also has a strong vasoconstrictor effect. This action is mediated via V_1 receptor.

Epinephrine & Norepinephrine:

Secretion:

Both hormones are secreted from the adrenal medulla.

body except arterioles → coronary
→ liver
→ skeletal m.s.

lipolysis

Secretion is increased by:

- (1) Diffuse sympathetic stimulation during emergency conditions.
- (2) Emotional stress.
- (3) Hypoglycemia.
- (4) Hypothermia & exposure to cold.
- (5) Hypotension.

Emotion
Emergency

HYPG ← glycemia
thermia
tension

Vascular effects of epinephrine:

- Dilates the blood vessels in skeletal muscle and the liver via β_2 receptors.
- This action usually overbalances the vasoconstrictor effects of epinephrine (α_1) in other places.
- The total peripheral resistance (TPR) drops.

Vascular effects of norepinephrine:

Produces vasoconstriction in almost all organs via α_1 receptors

Renin-Angiotensin System (RAS):

- Renin-angiotensin system plays a central role in the physiology and pathophysiology of the cardiovascular system
- Most of the effects of RAS are mediated by angiotensin II.



angiotensinogen → go blood

Formation of angiotensin II takes place in 2 steps:

1- Renin is a proteolytic enzyme. It acts on hepatic angiotensinogen to form angiotensin I (decapeptide).

Renin is secreted from the juxta-glomerular apparatus of the kidney.

Its secretion is increased by:

- (a) Hypovolemia and hypotension. (1)
- (b) Renal ischemia (e.g. renal artery stenosis). (2)
- (c) Decreased Na^+ delivery to distal tubule of the nephron. (3)
- (d) Sympathetic stimulation (via β_1 adreno-receptors). (4)

↓ No reabsorption
↓ water reabsorption
→ kidney II

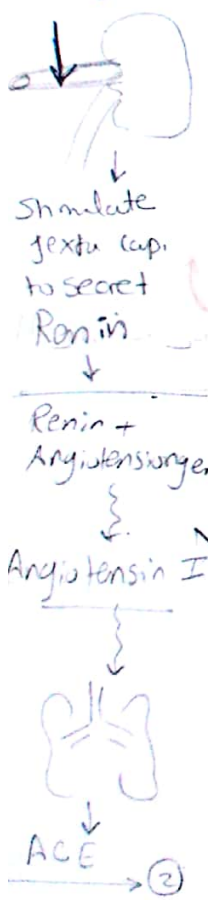
2- Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II (octapeptide).

ACE is found in the endothelial cells of blood vessels including those of the lung.

Less than 10 % of the ACE is freely circulating in blood and the remaining 90 % of ACE is found locally as tissue membrane bound enzyme.

Angiotensin II receptors: 2 cell surface receptors:

- a- Angiotensin II receptor type 1 (AT_1) which is widespread and mediates most of the actions of the angiotensin II in adult tissues
- b- Angiotensin II receptor type 2 (AT_2) which is less spread than AT_1 .



AT₂ receptor has physiological effects that counterbalance those of AT₁ receptor.

Actions of angiotensin II:

Actions mediated via AT₁

Main actions:

1- Peripheral vasoconstriction:

a- Arterioles: ++ TPR

b- Veins: ++ VR → ++ COP

2- Increasing Na⁺ reabsorption by distal renal tubules:

a- ++ secretion of aldosterone from adrenal cortex indirect

b- Direct action on distal renal tubule.

1 & 2 → ++ ABP

Other actions:

③ Inhibition of renin secretion by -ve feed back mechanism.

4- Sympathetic stimulation and increased catecholamines secretion.

5- Vasopressin secretion to decrease water loss in urine.

6- Stimulation of thirst center to increase water intake.

-ve
Renin

Note: Angiotensin III (which is produced by enzymatic removal of one amino acid from angiotensin II) has 100 % of aldosterone stimulating effect and only 40% of the vasoconstrictor effect of angiotensin II.

Actions mediated via AT₂:

1- Vasodilatation.

2- Diuresis (increase water excretion by the kidneys).

3- Natriuresis (increase Na⁺ excretion by the kidneys).

4- Apoptosis (programmed cell death).

Two classes of drugs are used to inhibit the RAS system:

① Angiotensin-converting enzyme inhibitors (ACE-Is) that inhibit conversion of angiotensin I to angiotensin II.

② Angiotensin receptor blockers (ARBs) that block the AT₁ receptor.

1 & 2 are used in treatment of hypertension.

Kinins:

- Two types of kinin are known:

① Bradykinin (nonapeptide i.e. formed of 9 amino acids).

② Lysyl bradykinin (decapeptide i.e. formed of 10 amino acids).

- * 2 types: Bradykinin, Lysyl Bradykinin
- * HMWK, LMWK $\xrightarrow{\text{tissue kallikrein}}$ Lysyl Kinin
- * HMWK $\xrightarrow{\text{plasma kallikrein}}$ Bradykinin
- * Prekallikrein $\xrightarrow{2 + \text{Plasmin}}$ plasma Kallikrein

* Kinins are present mainly in tissues, but small amounts are also found in the circulating blood. (as the Kallikreins)

- Two precursors: high-molecular-weight (HMW) kininogen and low-molecular-weight (LMW) kininogen form kinins.

- Two protease enzymes are responsible for the formation of kinins from their precursors:

1- Tissue kallikrein: acts on both HMW & LMW kininogens forming lysyl bradykinin.

2- Plasma kallikrein: acts on HMW kininogen to form bradykinin.

Note: plasma kallikrein circulates in blood as prekallikrein.

It is activated by "prekallikrein activator":

This activator is a part of active clotting factor XIIa. It is formed by the action of plasmin (fibrinolysin) on XIIa

- Two types of receptors for kinins: B₁ and B₂ receptors. (B₂ Bradykinin)

- Two kinases metabolize kinins to inactive fragments: kininase I and kininase II enzymes. Kininase II is the same enzyme as angiotensin II converting enzyme (ACE).

Actions:

- Kinins (acting on B₂ receptors) have the following functions (generally similar to histamine):

- 1- They relax VSMCs, and lower blood pressure via NO release. (1)
- 2- Contraction of plain muscles of viscera. (5)
- 3- Increase capillary permeability. (3)
- 4- Positive chemotactic effect. (4)
- 5- Stimulate pain receptors via B₁ receptors. (2)

Natriuretic hormones:

- Three natriuretic hormones are known in humans:

- 1- Atrial natriuretic peptide (ANP) released by atrial myocytes.
- 2- Brain natriuretic peptide (BNP) released by myocytes of ventricles of the heart. It is also synthesized in the brain. (both from ventricles)
- 3- C-type natriuretic peptide (CNP) present in vascular endothelial cells, the brain and kidney.

Renin secretion (الانجوتنسين) inhibit

Angiotensin II
Natriuretic

- Three types of natriuretic peptides receptors (NPR) are present:

- 1- NPR-A: Which has the greatest affinity for ANP
- 2- NPR-B: which has the greatest affinity for CNP
- 3- NPR-C: can bind the three natriuretic peptides.

- Three main actions: -- blood volume and in turn -- CVP, -- COP & -- ABP. They also counter the blood pressure-raising effects of the renin-angiotensin system via:

(A) Vascular actions:

- 1- Relaxation of VSMCs by receptor-mediated elevation of cGMP. NO
- 2- Inhibition of the vasoconstrictor effect of catecholamines.
- 3- Inhibition of the vasoconstrictor effect of angiotensin II.

(B) Renal actions:

- 4- Increase sodium excretion.
- 5- Inhibition of the conversion of pro-renin to rennin.
- 6- Inhibits the action of aldosterone (inhibits the action of Na^+/K^+ ATPase).

(C) Adrenal action:

- 7- Inhibition of aldosterone secretion by adrenal cortex.

Secretion:

Natriuretic peptides secretion is increase by:

- ① Stretch of atrial muscle fibers: i.e. ++ ECF volume is (e.g., ingestion of high-salt diet, and by immersion of the body in water up to the neck). This increases venous return and CVP.
- ② Raised sodium concentration in extracellular fluid.
- ③ Sympathetic stimulation of β -adrenoceptors.
- ④ Angiotensin-II.
- ⑤ Endothelin-I.

IV- Systemic Regulation by the Nervous System

All blood vessels, except capillaries and venules, contain vascular smooth muscle cells and receive motor nerves from the sympathetic.

The sympathetic fibers to:

- a- The resistance vessels (small arteries and arterioles) regulate the tissue blood flow and arterial blood pressure.
- b- The venous capacitance vessels change the volume of blood stored in the veins.

Innervation of blood vessels

A) Vasoconstrictor fibers:

1- Noradrenergic sympathetic vasoconstrictor fibers:

- End on most blood vessels in the body.
- Are vasoconstrictor in function.
- Have tonic activity i.e. continuous discharge (Vasomotor tone) creating the total peripheral resistance and regulating arterial blood pressure.

B) Vasodilator fibers:

2- Cholinergic sympathetic vasodilator fibers.

- End mainly on resistance vessels of the skeletal muscles. *liver*
- Are vasodilator in function

3- Parasympathetic vasodilator fibers:

Parasympathetic nerve fibers that are definitely true vasodilator are those supplying genital erectile tissue.

4- Sensory nerves near blood vessels (Antidromic impulses):

Afferent sensory impulses from the skin relay antidromically via branch of the sensory nerve innervating a blood vessel.

These antidromic impulses release substance P that produces vasodilation through "local axon reflex". *false Reflex* *وسيلة*

Sympathetic tone → In most tissues, nerve-mediated vasodilation is produced by decreasing the rate of tonic discharge in the vasoconstrictor nerves.

Symp. vasodilator system → In skeletal muscles, vasodilation can also be produced by activating the sympathetic vasodilator system. *(emergency)*

Summary of factors affecting the caliber of the arterioles:

	Constriction	Dilatation
Local factors:	- Decreased local temperature. - Autoregulation	- Increased CO₂, and decreased O₂ - Increased K⁺, adenosine, lactate, - Increased local temperature.
Endothelial products:	- Endothelin-1 - Angiotensin II. - Thromboxane A2	- Nitric oxide (NO) - Kinins (bradykinin) - Prostacyclin
Circulating hormones:	- Epinephrine (except in skeletal muscle and liver) - Norepinephrine - Vasopressin - Angiotensin II	- Epinephrine in skeletal muscle and liver. - Substance P - Histamine - Atrial natriuretic peptide
Neural factors:	- Increased discharge of noradrenergic vasomotor	- Decreased discharge of noradrenergic vasomotor

	nerves	nerves. - Activation of cholinergic dilator fibers to skeletal muscle.
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Regulation of arterial blood pressure

Three groups of mechanisms that differ in their time course:

1- Rapidly induced mechanisms: act within seconds to few minutes.
These are nervous mechanisms (a group of reflexes).

2- Intermediate mechanisms: develop over minutes to hours:
a- Stress-relaxation response of resistance vessels.
b- Capillary fluid-shift response.
c- Renin-angiotensin system.

3- Long term mechanisms: develop over several days
Important in longer-term blood pressure control
a- Renal pressure natriuresis.
b- Aldosterone secretion.

Nervous (rapid) regulation of ABP

The centers of these reflexes are present in medulla oblongata.

These medullary centers are the "vasomotor area" and the "cardiac inhibitory area"

I- Vasomotor area:

- Located in the rostral ventrolateral medulla (RVLM).
 - Contains neurons that mediate sympathetic discharge to blood vessels and heart.
 - Neurons discharge directly to sympathetic preganglionic neurons in the intermediolateral gray column (IML) of the spinal cord.
- Postganglionic noradrenergic neurons innervate the heart and blood vessels.
- Receives inhibitory fibers from nucleus of the tractus solitarius (NTS).
 - Stimulation of vasomotor area leads to elevation of arterial blood pressure through the following mechanisms:

A) On blood vessels:

- 1- Arteriolar constriction (vasomotor tone): ++ TPR
- 2- Venoconstriction (venomotor tone): ++ VR → ++ COP

B) On heart:

- 3- ++ HR & ++ SV → ++ COP

4- Associated - - in Vagal tone to the heart $\rightarrow$ $++$ HR

Note: $ABP = TPR \times SV \times HR$

II- Cardiac inhibitory area:

- Located in the dorsal motor nucleus of the vagus and in the nucleus ambiguus.
- Contains neurons that mediate vagal discharge to the heart.
- Receive excitatory fibers from the nucleus tractus solitarius (NTS).
- Stimulation of this area decreases heart rate and cardiac output.

Afferents to the medullary cardiovascular areas

- Neurons of the vasomotor and cardiac inhibitory areas receive afferents that $++$ or $---$ their activity.
- The aim is to control the level of arterial blood pressure.
- Afferents that stimulate vasomotor area will inhibit the cardiac inhibitory area at the same time, and vice versa.

Afferents to the medullary cardiovascular come from the following sites:

- I. Arterial baroreceptors) high-pressure baroreceptors).
- II. Cardio-pulmonary stretch receptors (Low-pressure receptors).
- III. Central chemoreceptors and from the carotid and aortic chemoreceptors (peripheral chemoreceptors)
- IV. Left ventricles.
- V. Lungs.
- VI. Higher brain centers.
- VII. Somatic afferents.

In addition, the activity of medullary cardiovascular areas is affected by direct effects of hypoxia and hypercapnia.

I. Arterial baroreceptors (high-pressure baroreceptors):

These are mechanical stretch receptors.

They act as "pressure sensor" that monitor the level of ABP.

Site:

- Carotid sinus (small dilatation of the internal carotid).
- Aortic arch.

Innervation:

- Carotid sinus nerve (Hering's nerve) is a branch of the glossopharyngeal nerve (IX cranial nerve).
- Aortic nerve (branch of vagus, X cranial nerve).

- They are known as "buffer nerves" and they end in the nucleus of tractus solitarius.

Stimulation:

Arterial baroreceptors are stimulated by:

- 1- Arterial blood pressure.

The threshold for baroreceptors stimulation is 50 mmHg.
Higher pressure produces more discharge from baroreceptors.

Maximal discharge rate occurs at 160 mmHg.

Above that, no further increase in discharge rate occurs.

- 2- Pulse pressure: higher pulse pressure causes more stimulation of baroreceptors than low pulse pressure.

Function: Baroreceptor reflex:

Compensate for sudden changes in ABP e.g. due to change in posture or hemorrhage.

- 1- At normal mean ABP (90 mmHg), baroreceptors are stimulated and send low rate tonic impulses to the nucleus of tractus solitarius (NTS).

Neurons of NTS send:

- a- Inhibitory signals to vasomotor area
- b- Excitatory signals to cardiac inhibitory area.

2- When arterial blood pressure increases:

Tonic discharge from baroreceptors to NTS is increased, this will lead to:

- a- More inhibition of vasomotor area which -- sympathetic discharge to:

- i) The heart: -- HR, SV & COP

- ii) The blood vessels:

- VD of veins → -- VR

- VD of arterioles → -- TPR.

However, in long term hypertension, the sensitivity of baroreceptors reflex decreases & function to maintain arterial blood pressure at this higher level i.e. resetting of baroreceptors reflex. This reflex plays insignificant role in defense against hypertension.

- b- More excitation of cardiac inhibitory area ++ Vagal tone to the heart → -- HR → -- COP → -- ABP

3- When arterial blood pressure decreases: the reverse occurs.

N.B.:

Carotid sinus syndrome:

Some people have very sensitive carotid sinus baroreceptors.

If external pressure is applied to the carotid sinus (e.g. by tight collar or during shaving) the reflex is activated leading to marked --- ABP.

This may cause cerebral ischemia and fainting.

Denervation of the carotid sinus cures this condition.

II. Atrial (volume) receptors = (cardio-pulmonary stretch receptors) = (low-pressure receptors):

These are stretch receptors present in the low-pressure side of the circulation.

Site:

Located in the walls of the right and left atria at the entrance of super vena cava (svc) and inferior vena cava (IVC) and in the wall of the pulmonary veins and pulmonary circulation

Stimulation:

Atrial stretch receptor (volume receptors) respond to distension of the atrial walls. The discharge is increased when ++ VR, CVP or blood volume is ++ & vice versa.

Innervation:

Vagal nerve fibers

Function: "Atrial volume reflex":

When atrial volume receptors are stimulated, the following reflex effects occur:

a- Systemic vasodilatation

b- Heart rate increased rather than decreased.

Bainbridge reflex: rapid infusion of large volume of blood or saline solution in anaesthetized animals produces tachycardia only if the initial heart rate is slow. The reflex is mediated via vagi. The physiological role of this reflex is to achieve pumping of the increased venous return without marked elevation of cardiac preload. The reflex prevents accumulation of blood in atria and pulmonary vessels that could otherwise lead to pulmonary edema.

c- It decreases the secretion of vasopressin.

d- ++ The secretion of atrial natriuretic peptide, rennin and aldosterone.

These changes play a major role in intermediate-time course and long-term regulation of arterial blood pressure.

III. Peripheral chemoreceptors:

Site:

Located in carotid and aortic bodies

Innervation:

From carotid bodies by carotid sinus nerve (branch of the IX cranial nerve) and by the vagus nerve from aortic bodies

Stimulation:

- Chemoreceptors are primarily concerned with respiratory regulation.

They are more sensitive to low PO_2 than high PCO_2 or low pH (high H^+ concentration).

- However, if ABP is markedly decreased to 40-60 mmHg, blood flow in carotid and aortic bodies decreases.

This leads to hypoxia and stimulation of the peripheral chemoreceptors.

Response:

Bradycardia and vasoconstriction

However, in hemorrhage, systemic hypoxia stimulates respiration and increase catecholamines secretion both of which produce tachycardia & cancel the bradycardia produced by chemoreceptor stimulation.

The overall effect is therefore vasoconstriction and elevation of blood pressure.

Mayer waves:

These are cyclic fluctuation in ABP that occur once every 20-40 seconds in hypotensive patients.

Hypotension leads to ischemia and stimulation of peripheral chemoreceptors. This results in elevation of arterial blood pressure, which will improve blood flow to peripheral chemoreceptors. The stimulus on the receptors is eliminated so blood pressure decreases and the cycle repeats itself.

Direct effect of changes in blood gases on arterial blood pressure:

Hypercapnia, and to a lesser extent hypoxia, directly stimulate the vasomotor area leading to elevation of ABP.

The Central nervous system (CNS) ischemic response:

-- ABP (hypotension) leads to ischemia of the medullary vasomotor area.

Local PCO_2 rises which stimulates the vasomotor area → marked VC and

++ ABP associated by bradycardia due to baroreceptor reflex.

The reflex is the most powerful stimulus of the sympathetic nervous system & is excited only when ABP drops below 50 mmHg.

Cushing reflex:

++ Intracranial pressure → ++ ABP & -- HR

Mechanism:

High intracranial pressure compresses cerebral blood vessels causing brain ischemia.

Hypercapnia and hypoxia which stimulates:

a- Vasomotor area → ++ ABP

b- Stimulation of cardiac inhibitory area plus stimulation of baroreceptors by ++ ABP → -- HR.

IV. Left ventricles (Coronary chemo reflex):

Site:

Receptors present in the wall of the left ventricle that when stimulated, produce -- HR & -- ABP.

Stimulus:

1- Marked stretch is needed to stimulate these receptors so that their physiological significance is doubted.

2- Injection of some drugs (e.g. serotonin and veratridine) in branches of the left coronary artery.

Innervation:

Impulses are carried by the vagus nerve.

Response:

Transient apnea, followed by rapid breathing, bradycardia and hypotension. The physiological significance of this reflex is unsettled. However, in cases of myocardial infarction the damaged tissues release substances that stimulate left ventricular receptors → the hypotension frequently observed in these cases (Bezold- Jarish reflex coronary chemoreflex) thus, left ventricular receptors act as mechano & chemoreceptors.

V. Lungs (Pulmonary chemoreflex):

Site:

C-fiber endings are close to pulmonary vessels and are called J-receptors (juxtacapillary receptors).

Stimuli & response:

1- Injection of serotonin and other drugs such as capsaicin and veratridine into the pulmonary artery leading to apnea followed by rapid breathing, hypotension and bradycardia.

2- Also stimulated by hyperinflation of the lung, pulmonary edema, congestion and embolism → rapid breathing, bradycardia and hypotension.

Innervation:

Vagal nerve fibers

VI. Higher brain centers:

Impulses arising from the cerebral cortex (especially the limbic lobe and prefrontal area) reach the hypothalamus.

Neurons of the hypothalamus discharge to produce:

- a- Stimulation of vasomotor area leading to ++ HR & ++ ABP e.g. during emotions and at the beginning of muscular exercise.
- b- Direct stimulation of spinal cholinergic sympathetic neurons of LHCs (without relay at medullary centers).

It is responsible for VD of muscle arterioles before the beginning of muscular exercise

VII. Somatic afferents:

They can affect arterial blood pressure.

This is known as "the somatosympathetic reflex".

These afferents arise from:

a- Pain receptors:

- 1- Cutaneous pain → ++ HR, ++ ABP & release of adrenaline.
- 2- Visceral pain has an opposite effect (hypotension).

b- Thermal skin receptors:

- 1- Exposure to cold, ++ ABP
- 2- Exposure to warmth: -- ABP

c- Muscle proprioceptors: during exercise ++ ABP & ++ HR

Intermediate time course mechanisms

I. Stress Relaxation:

Definition:

It is a property of blood vessels (& other tissues) related to their viscolastic properties and not to their contractile properties.

This property minimizes P changes with blood pressure changes.

e.g.

- If the volume of blood increases circulatory filling pressure, VR, COP & ABP initially rises.
- After minutes the circulatory filling & ABP gradually decreases to a lower value.

Mechanism:

It is due to decreased wall tension, as shown from the law of Laplace.

Pressure = Tension X radius

Decline of pressure with constant volume (i.e. radius is not changed) should be due to decreased wall tension.

Importance:

Defense against the effect of sudden changes in blood volume on arterial blood pressure

Note:

The mechanism also operates in the opposite direction: i.e. with sudden decrease in blood volume.

II. Capillary Fluid Shift Mechanism

It minimizes the effect of changing volume on ABP.

e.g. If blood volume increases, blood pressure will also rise. However, increased blood volume leads also to rise of capillary hydrostatic pressure. This favors more filtration. Thus, blood volume decreases. Venous return and cardiac output decreases. The rise in arterial blood pressure is minimized & vice versa.

III. Renin - Angiotensin System (RAS) vasoconstriction:

Decrease arterial blood pressure (ABP) and hypovolemia activate RAS. Activation of RAS and formation of angiotensin II takes about 20-30 minutes.

Angiotensin II raises arterial blood pressure by direct vasoconstrictor action and by activation of the sympathetic discharge (Discussed before).

Long Term Regulation of Arterial Pressure**Renal - body fluids mechanism**

Decreased ECF volume leads to decreased mean circulatory filling pressure, venous return, and cardiac output.

This causes arterial blood pressure to decrease. Increased ECF volume has opposite effects, leading to elevation of arterial blood pressure.

The renal-body fluids mechanism controls the level of arterial blood pressure by adjusting the volume of ECF & in turn, VR, COP & ABP.

Volume of the ECF represents a balance between:

- Na⁺ and water intake in diet.
- Na⁺ and water excretion by kidneys.

Sodium intake is not tightly controlled in humans.

Therefore, Na⁺ balance and consequently ECF volume are maintained mainly by regulation of renal Na⁺ excretion by the following mechanisms:

1- Renal pressure natriuresis:

i.e. ++ ABP → ++ renal Na & H₂O excretion → -- volume of ECF and --- ABP to normal level & vice versa
This mechanism is very powerful and is the basic and most important mechanism for long-term regulation of ABP

2- Renin-angiotensin-aldosterone system:

Angiotensin II has an important role in long-term regulation of ABP.
If ABP -- → ++ Angiotensin II → -- Na⁺ and water excretion by the kidneys
a) Directly act
b) Via ++ aldosterone secretion
So ECF volume increases and arterial pressure rises to normal & vice versa.
It should be noticed that inhibition of rennin-angiotensin-aldosterone secretion enhances the activity of pressure natriuresis mechanism.

3) Atrial natriuretic peptides (ANP) secretion:

++ ECF volume → ++ secretion of ANP. ANP increases Na⁺ excretion by the kidney and the volume of ECF decreases to normal. Blood pressure returns to normal.
It should be noticed that ANP enhances the activity of pressure natriuresis mechanism.

4) Vasopressin secretion:

-- ECF volume results in -- discharge of atrial low-pressure receptors.
++ secretion of vasopressin → -- water excretion by the kidneys (water retention) ++ → ECF volume & ++ ABP

Hypertension (HTN)

Definition:

It is sustained elevation of the systemic ABP
Systolic ABP above 140 mmHg
Diastolic ABP above 90 mmHg

Types: two types of HTN are known:

- 1- Essential HTN "primary HTN" 93%: unknown cause.
- 2- Secondary HTN 7 % or less caused by renal, endocrine, or other causes.

Secondary HTN:

Secondary hypertension accounts for less than 5 % of all causes of hypertension.

Causes of secondary HTN:

a- Renal causes:

- Chronic renal disease.
- Renal artery stenosis.

b- Endocrinal causes:

- Primary hyperaldosteronism (increased secretion of aldosterone).
- Pheochromocytoma (tumor of adrenal medulla secreting catecholamines).
- Cushing's syndrome (increased secretion of cortisol).

c- Drug-induced hypertension:

Non-steroidal anti-inflammatory drugs

Glucocorticoids

Contraceptive pills

d- Coarctation of the aorta.

Prevalence rate in Egypt:

- 26.3 % of population above age of 25 year.
- 50 % of Egyptians above age of 60 years.

Classification of HTN:

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	<130	<85
High-normal	130-139	85-89
Grade 1 (mild hypertension)	140-159	90-99
Grade 2 (moderate hypertension)	160-179	100-109
Grade 3 (severe hypertension)	>180	>110
Isolated systolic hypertension	>140	<90

Diagnosis of hypertension:

- Diagnosis of HTN is based upon at least 5 office visits over a period varying from days to months.
- Blood pressure should be measured accurately and under standardized conditions.

Control of heart rate

- In general: stimuli that increase the heart rate also increase the BP and, those that decrease the heart rate lower the BP.
- There are two exceptions:
 - 1) Stimulation of atrial stretch receptors produces hypotension and tachycardia.
 - 2) Increased intracranial pressure produces hypertension and, bradycardia.

Factors that increase heart rate:	Factors that decrease heart rate:
- Decreased activity of arterial baroreceptors. - Increased activity of atrial stretch receptors. - Inspiration - Excitement - Anger (irritation). - Most painful stimuli. - Hypoxia - Exercise. - Epinephrine. - Thyroid hormones. - Fever	- Increased activity of arterial baroreceptors - Expiration - Fear (be afraid of) - Stimulation of pain fibers in trigeminal nerve (CN V) - Norepinephrine - Increased intracranial pressure

Circulatory shock

Definition:

It is a state of inadequate tissue perfusion with a relatively or absolutely inadequate cardiac output.

Types of circulatory shock (According to the cause):

I) Hypovolemic shock:

Cause: decreased blood volume.

Examples of this type of shock are:

- a- Hemorrhagic & traumatic shock: due to external or internal bleeding
- b- Burns: due to loss of plasma.
- c- Dehydration: excessive loss of fluid e.g. due to severe persistent vomiting and diarrhea.
- d- Surgical shock: seen in patients undergoing surgery. Bleeding may be external and/or internal in addition to dehydration.

II) Low-resistance shock:

Cause: increased capacity of the vascular system (marked vasodilatation).

Examples of this type of shock are:

- a- Neurogenic shock: caused for example by strong emotions.
- b- Anaphylactic shock: due to excessive allergic reaction leading to release of histamine (strong vasodilator).
- c- Septic shock: this occurs in severe infections, and is due to release of bacterial toxins.

III) Cardiogenic shock:

Cause: impairment of myocardial pumping → -- COP

Examples of this type of shock are:

- a- Myocardial infarction: myocardial contraction is much reduced.
- b- Arrhythmias: very rapid or very slow arrhythmias

IV) Obstructive shock:

Cause: obstruction to blood flow to or from the heart.

Examples of this type of shock are:

- a- Tension pneumothorax: venous return to the heart is impeded.
- b- Massive pulmonary embolism: output of the right ventricle is obstructed.
- c- Cardiac tamponade: compression of the heart by the pericardial fluid (e.g. bleeding inside the pericardial sac).
- d- Tight stenosis of cardiac valves.

Hemorrhagic Shock

Manifestations:

Vital signs:

- 1- ABP: hypotension (due to decreased venous return and cardiac output).
- 2- Pulse: rapid (due to reflex increased sympathetic activity) & weak (due to decreased pulse pressure).
- 3- Respiration: rapid (mainly due to stimuli of peripheral chemoreceptors).
- 4- Temp: cold pale clammy skin (due to cutaneous vasoconstriction and increased sweat secretion caused by increased sympathetic stimulation).

Others:

- 5- Thirst (due to the action of angiotensin II and baroreceptors-mediated response).
- 6- Reduced urine formation (oliguria) due to decreased renal blood flow.
- 7- Acidosis (due to tissue hypoxia that leads to anaerobic glycolysis and production of excess lactic acid).
- 8- Restlessness and apprehension. This is due to the action of catecholamines on the reticular formation of the brain.

Note: Deterioration of the level of consciousness that may reach coma occurs in severe cases of shock due to acidosis and cerebral ischemia.

Compensatory reactions to hemorrhagic shock:

These reactions involve both rapid and slow compensatory mechanisms:

1- Rapid compensatory reactions:

Aim: maintain arterial blood pressure to keep normal blood supply to the brain and myocardium. This is achieved by decreasing blood flow to other less vital parts of the body.

2- Long-term compensatory reaction

Aim: to restore blood volume to normal, thus blood pressure can be maintained at normal level with normal blood flow to all tissues.

Rapid compensatory reactions to Hemorrhage:

These responses include:

A- Neural mechanisms:

B- Humoral mechanisms:

A- Neural Mechanisms:

In hemorrhagic shock there:

1- Decreased discharge of arterial baroreceptors due to low arterial blood pressure.

2- Decreased discharge of atrial volume receptors due to decreased blood volume.

3- Stimulation of peripheral chemoreceptors due to decrease in their blood flow rate leading to their hypoxia.

These changes lead to stimulation of medullary vasomotor area with consequent increased activity of sympathetic discharge leading to elevation of arterial blood pressure as follows:

a- Increase heart rate and force of myocardial contraction

Cardiac output increases and arterial blood pressure (ABP) rises.

b- Vasoconstriction of arterioles → ++ TPR → ++ ABP

- Vasoconstriction of skin vessels makes it cold and pale.

- Vasoconstriction of renal vessels decreases glomerular filtration rate. Urine formation decreases (oliguria).

Note: vasoconstriction of renal vessels may be so severe that it may lead to damage of renal tubules and renal failure.

- Coronary vessels are dilated due to increased cardiac work.

- Cerebral vessels are not constricted; therefore cerebral blood flow is constant.

c- Vasoconstriction of veins $\rightarrow$ $\uparrow$ mean systemic filling P $\rightarrow$ $\uparrow$ VR $\rightarrow$ $\uparrow$ COP $\rightarrow$ $\uparrow$ ABP

In addition, stimulation of peripheral chemoreceptors stimulates respiration. This may help increasing venous return (respiratory suction).

B) Humoral Mechanisms:

1- $\uparrow$ Catecholamines secretion:

Cause: hypotension.

However, the role of catecholamines in raising ABP is limited.

Catecholamines stimulate the reticular formation of the brain stem.

This is responsible for stimulation of respiration and restlessness seen in shocked patients.

2- $\uparrow$ Angiotensin II:

Cause renal ischemia.

Angiotensin II helps correction of shock state by:

a- Renal $\uparrow$ Na & H₂O reabsorption (directly & via $\uparrow$ aldosterone)

b- Vasoconstriction of arterioles & veins.

c- Stimulation of thirst sensation.

Drinking helps to restore extracellular fluid (ECF) volume

3- Vasopressin secretion:

Cause: decreased discharge from atrial volume receptors.

It enhances retention of water by the kidneys.

Thus, it helps to restore ECF volume

Long-term compensatory reactions:

1- Correction of plasma volume:

After moderate hemorrhage, correction of plasma volume takes about 12-72 hours. The following mechanisms are involved:

a- Tissue fluid shift: after hemorrhage, capillary hydrostatic pressure is decreased. Interstitial fluid moves into the capillaries and plasma volume is increased.

b- Thirst sensation.

c- Aldosterone secretion:

- This occurs in response to high angiotensin II and ACTH in plasma.

- Aldosterone increases Na⁺ reabsorption by the renal tubules, retention of Na⁺ increases plasma and interstitial fluid volume.

d- ADH (vasopressin) secretion.

2- Correction of plasma proteins:

- a- Shortly after hemorrhage, performed albumin enters the blood from extravascular stores.
- b- Complete restoration of plasma proteins depends on hepatic synthesis and takes 3-4 days to be complete.

3- Correction of red cell mass:

Hemorrhage leads to ischemia and hypoxia of kidneys and liver.

This triggers the secretion of erythropoietin, which stimulates RBCs formation by bone marrow.

It takes 4-8 week to restore RBCs to normal.

Outcome of shock state:

The fate of patients with hemorrhagic shock depends largely on the volume and rate of blood loss.

The following may occur:

- 1- Patient may recover completely due to the compensatory responses aided by proper treatment (mainly transfusion).
- 2- Patient may die rapidly if compensatory responses and medical aid were not able to correct the effects of hemorrhage.
- 3- Some patients pass to a state known as refractory shock.

Treatment of shock:

1- Removal of the cause of shock: e.g. stoppage of bleeding.

2- Patient is put in supine position with the feet raised to help venous return.

Sitting and standing should be avoided.

3- Restoration of blood volume:

a- Blood transfusion: this is optimal for hemorrhagic shock.

b- Plasma transfusion: is in cases of shock due to burn or injuries.

Plasma expanders (high molecular weight polysaccharides e.g. dextran solution) can be used instead.

c- Concentrated human albumin: expands plasma volume by drawing fluid from interstitial space. It has the disadvantage of increasing tissue dehydration.

4- Drugs:

a- Vasopressor drugs can elevate arterial pressure.

However, their use should be discontinued as soon as possible since they decrease blood flow to other parts of the body.

- b- Dopamine is useful in cardiogenic and traumatic shock because it has positive inotropic effect and is vasodilator to renal vessels, whereas it produces vasoconstriction elsewhere.
- c- Epinephrine is very useful in treatment of anaphylactic shock.
- d- Glucocorticoids help in treatment of shock since they decrease capillary permeability.

Refractory shock:

It is resistant to treatment.

Cardiac output remains low even if blood volume is restored to normal.

Mechanisms responsible for development of refractory shock include:

1- Spasm of precapillary sphincters and venules especially in splanchnic region. The following sequence occurs:

- a. Tissues damage occurs: this is caused by hypoxia resulting from decreased tissue blood flow.
- b- After 3-5 hours, precapillary sphincters dilate while venules remain constricted.
- c. Capillary hydrostatic pressure rises leading to excessive filtration of fluids.
- This leads to further decrease in blood volume.
- d. Granulocytes adhere to the injured capillary walls and release free oxygen radicals that produce more tissue damage.
- e. Bacteria enter the blood through injured vessels. Bacterial toxins are strong vasodilators.

2- Severe cerebral ischemia:

Marked decrease in ABP leads to marked cerebral ischemia. Ischemia leads to failure of vasomotor center.

This leads to slowing of the heart and vasodilatation.

Arterial pressure is further decreased leading to more cerebral ischemia.

This is a deadly positive feedback mechanism.

3- Severe cardiac ischemia:

Marked decrease in ABP leads myocardial ischemia in spite of coronary dilatation. Cardiac output decreases.

This leads to further decrease in ABP which makes the myocardium more ischemia.

This is a deadly positive feedback mechanism.

Special circulations

Coronary circulation

Anatomical considerations:

Coronary arteries: Right & left

The right coronary supplies the right ventricle and posterior wall of the left ventricle.

The left coronary supplies the anterior and lateral wall of the left ventricle. Both arteries arise from sinuses (small dilatation) in the root of the ascending aorta, behind two of the cusps of the aortic valve.

- The major coronary vessels lie on the epicardial surface of the heart and function as low resistance, distribution vessels.

These epicardial arteries branch into smaller arteries that dive into the myocardium and branch into smaller vessels and finally into capillaries

These intra-myocardial vessels become compressed when the myocardium contract. This compression affects the sub-endocardial vessels more than the sub-epicardial vessels.

- Capillary density in the myocardium is about $3000-4000/\text{mm}^2$. This is much higher than the corresponding value in skeletal muscle ($500-2000/\text{mm}^2$).

- Collateral circulation: there is no anastomosis between main coronary vessels. However, there is significant anastomosis between smaller coronary vessels.

- Venous drainage:

i- Coronary sinus and anterior coronary veins: these drain most of the coronary venous blood into the right atrium.

ii- Arterioluminal and Thebesian vessels drain the myocardium directly into different chambers of the heart.

Coronary blood flow:

- Under resting conditions, the coronary blood flow is about 250 ml/min ($84\text{ml}/100\text{ gram}/\text{min}$). This flow is much higher than skeletal muscle flow ($2.7\text{ml}/100\text{ gram}/\text{min}$)

- The right coronary artery receives bigger flow in 50% of people. On the other hand, in 20% of people the left coronary receives the bigger flow, whereas the flow in right and left coronaries is equal in 30% of people.

- The myocardial O_2 requirements are high ($9.7\text{ml}/100\text{gram}/\text{min}$).

As compared to skeletal muscle O_2 requirements at rest ($0.2\text{ml}/100\text{gram}/\text{min}$)

- The myocardium obtains its resting O_2 requirements by extraction of 70-80% of the O_2 delivered to it by coronary blood flow.

This near maximal extraction of O_2 is aided by the high number of capillaries in cardiac muscle.

In addition, all capillaries are open, i.e. there is no vasomotion in cardiac capillaries.

- Therefore, any increase in O_2 demand e.g. during exercise, cannot depend on increasing extraction of O_2 . Instead, coronary blood flow must increase to supply the extra O_2 needed.

Determinants (regulation) of coronary blood flow:

Coronary blood flow is determined by two factors:

A) Coronary perfusion pressure:

The perfusion pressure of the coronary vessels is the difference between aortic pressure and ventricular pressure (not coronary venous pressure). This gradient depends on:

- i- Aortic pressure: which changes during phases of cardiac cycle
- ii- Ventricular pressure: which is ++ to it maximal during systole

Regulation of coronary perfusion pressure (mechanical factors):

Left ventricular coronary flow:

During systole:

Left ventricular pressure reaches 121mmHg while aortic pressure reaches 120mmHg . The gradient for coronary flow is almost zero especially for sub-endocardial vessels.

Note: the sub-epicardial vessels are less compressed. The overall effect is small coronary flow during systole. Minimal CBF occurs during isometric contraction phase.

During diastole:

Left ventricular pressure decreases to zero mmHg while aortic pressure decreases to 80mmHg . The gradient for coronary flow is 80mmHg .

The maximal coronary flow occurs during early diastole (isovolumetric relaxation phase) when aortic pressure is still high.

Right ventricular coronary flow:

During systole:

Right ventricular pressure reaches 25mmHg while aortic pressure reaches 120mmHg . The gradient for coronary flow is 95mmHg .

During diastole:

Right ventricular pressure decreases to zero mmHg while aortic pressure decreases to 80 mmHg. The gradient for coronary flow is 80 mmHg. Therefore, coronary flow in the right ventricle occurs throughout the cardiac cycle and is maximal during ventricular systole.

B) Coronary vascular resistance:

Coronary vascular resistance is affected by different neural and chemical factors.

Regulation of coronary vascular resistance:

1- Metabolic regulation: increased metabolic activity of the heart (e.g. during exercise) produces coronary vasodilatation and increased CBF to match the increased O_2 requirements.

The metabolites responsible for this vasodilatation include CO_2 , K^+ , H^+ , prostaglandins and adenosine.

These metabolites activate a special type of K^+ channels (ATP-sensitive K^+ channels) in vascular smooth muscle of coronary vessels. This leads to hyperpolarization, relaxation of smooth muscles and vasodilatation.

2- Endothelial regulation:

The endothelium of the coronary vessels secrete:

- Vasodilator substances e.g. prostacyclin and nitric oxide (NO)
- Vasoconstrictor substances e.g. Endothelin-1

These substances are secreted in response to:

- Mechanical forces e.g. shear stress stimulates NO secretion.
- Nervous stimuli.
- Humoral stimuli.

3- Nervous regulation:

a- Sympathetic stimulation:

Coronary vessels contain both α and β adrenergic receptors.

- α adrenergic receptors stimulation causes vasoconstriction.
- β adrenergic receptors stimulation causes vasodilatation.

However, sympathetic stimuli of the heart increases heart rate and contractility leading to release of vasodilator metabolites.

Therefore, the overall effect of sympathetic stimulation of coronary vessels is vasodilatation.

b- Parasympathetic stimulation:

Coronary vessels have cholinergic receptors.

Stimulation of these receptors produces vasodilatation.

However, vagal stimulation of the heart causes bradycardia and decreases cardiac metabolism. This leads to coronary vasoconstriction.

4- Autoregulation:

Coronary circulation shows a considerable degree of autoregulation i.e. CBF is maintained constant with arterial perfusion pressure between 40-130mmHg.

Coronary autoregulation depends on myogenic response, local metabolites and substances released from the endothelium (e.g. adenosine and NO).

Measurements of coronary blood flow:

1- Kety method "Fick's principle":

Utilizing N₂O inhalation, cardiac catheter into the coronary sinus, and arterial blood samples

$$\text{Coronary BF} = Q_x \div ([A_x] - [V_x])$$

Where Q_x is the amount of N₂O taken by the heart per minute.

A_x is the arterial N₂O concentration

V_x is the coronary sinus venous N₂O concentration.

2- Radionuclides techniques:

Radionuclides such as Thallium 201 (²⁰¹Tl) are pumped into cardiac muscle cells by Na⁺-K⁺ ATPase. ²⁰¹Tl in cardiac muscle can be measured by radiation detector. ²⁰¹Tl distribution is directly proportionate to myocardial blood flow. Areas of ischemia can be detected by their low uptake as cold spots.

Radiopharmaceuticals such as technetium ^{99m} stannous pyrophosphate (^{99m}Tc-PYP) are selectively taken up by infarcted tissue and make infarcts stand as "hot spots" on scintiscans of the chest.

3- Coronary angiography (CAG):

Catheterization of the coronary arteries and injection of radio-opaque dye make it possible to image the coronary vessels and detect the site and degree of obstruction e.g. by a thrombus.

Pulmonary considerations

Anatomic considerations:

The lungs are the only organ in the body that receives the whole COP. All the pulmonary vessels are thin walled & contain less smooth muscle than the systemic circulation.

- Output of the right ventricle is carried to the lungs by the pulmonary artery.
- * Branches of the pulmonary artery run parallel to the bronchi down to the terminal bronchioles are called "extra-alveolar vessels".
- * Capillaries that surround the alveoli are called "alveolar vessels". These vessels are affected more by alveolar pressure.
- Bronchial arteries are branches of systemic circulation (they arise from aorta, subclavian, intercostals and internal mammary arteries). They supply the bronchial tree.
- 1/3 venous returns from bronchial vessels reaches the right atrium.
- 2/3 return via pulmonary veins to the left atrium.

Pressure, resistance and flow in pulmonary circulation:

- Pressures in the pulmonary circulation are much lower than the systemic circulation (low pressure circulation).
- Because of the low pressure in pulmonary capillaries, no filtration occurs in them.
- Pulmonary vascular resistance = $\Delta P/F = 7/5 = 1.4 \text{ mmHg/l/min}$ i.e. much less than systemic
- The main site of resistance in pulmonary circulation is the capillaries, not the arterioles as in systemic circulation.

Comparison between pressure in pulmonary and systemic circulation:

Pulmonary circulation	Systemic circulation
Right ventricular pressure:	Left ventricular pressure:
Systolic: 25 mmHg	Systolic: 120 mmHg
Diastolic: 0 mmHg	Diastolic: 0 mmHg
Pulmonary artery pressure:	Aortic pressure:
Systolic: 25 mmHg	Systolic: 120 mmHg
Diastolic: 10 mmHg	Diastolic: 80 mmHg
Mean: 15 mmHg	Mean: 90 mmHg
Functional capillary pressure: 10 mmHg	Functional capillary pressure: 25 mmHg
Left atrial pressure: 8 mmHg	Right atrial pressure: 0 mmHg
Perfusion pressure: 7 mmHg	Perfusion pressure: 90 mmHg

Regulation of pulmonary vascular resistance and pulmonary blood flow:

The following factors affect pulmonary vascular resistance:

1) Lung volume:

Pulmonary vascular resistance (PVR) is minimal at functional residual capacity (FRC) of the lung.

PVR increases when:

- The lung is inflated towards TLC (total lung capacity):

Intrapleural pressure decreases. The diameter of extra-alveolar vessels increases and their resistance decreases.

Alveoli expand. Alveolar vessels are compressed and their resistance increases.

The net effect is an increased PVR.

- Lung is deflated towards RV (residual volume):

Intrapleural pressure increases. The diameter of extra-alveolar vessels decreases and their resistance increases.

Alveoli collapse. Alveolar vessels are less compressed and their resistance decreases.

The net effect is an increased PVR.

2) Volume of blood pumped in pulmonary vessels:

PVR decreases as flow in the pulmonary vessels increases. This limits the rise of pressure.

The decrease of PVR when blood flow increases is due to:

- a- Distension of the thin-walled pulmonary vessels
- b- Recruitment of capillaries i.e. opening of closed capillaries.

3) Alveolar PO₂: "hypoxic vasoconstriction"

Unlike systemic vessels, pulmonary arterioles constrict in response to low PO₂.

When part of the lung is hypoxic e.g. due to obstruction of a bronchus, the arterioles supplying this are constrict so, blood shifts to the well ventilated parts of lungs.

4) Alveolar PCO₂:

High alveolar PCO₂ leads to pulmonary vasoconstriction.

This mechanism also decreases blood flow to poorly ventilated areas of the lung.

5) Autonomic innervation:

Sympathetic stimulation increases PVR and this leads to decreased pulmonary blood flow.

6) Vasoactive substances affecting pulmonary vessels:

Vasoconstrictor substances include norepinephrine, angiotensin II, histamine, serotonin and endothelins.

Vasodilator substances include acetylcholine, bradykinin, ANP, and nitric oxide.
In patients with pulmonary hypertension, there is deficiency of NO synthase enzyme.

Cerebral Circulation

Anatomic considerations:

- Arterial blood supply of the brain comes from:
 - Two internal carotid arteries
 - Two vertebral arteries which unite to form the basilar artery
 - Two internal carotid arteries and the basilar artery form the "circle of Willis" which gives rise to 6 main arteries to supply the two cerebral hemispheres, 3 arteries for each hemisphere.
- Most of the blood supply to the brain comes from the internal carotids. Each internal carotid supplies one hemisphere.
- Anastomosis between cerebral vessels is limited and functionally insignificant i.e. if one cerebral artery is blocked the anastomosis can not restore blood supply to the ischemic area.
- Capillaries are of the continuous (non-fenestrated type).
- Venous drainage: through deep cerebral veins and dural venous sinuses, which empty mainly in the internal jugular vein
- Innervation of cerebral vessels:
 - Three types of nerve supply to cerebral vessels exit:
 - 1- Sympathetic supply: comes from superior cervical ganglion. Their chemical transmitter is noradrenalin and neuropeptide Y.
 - 2- Parasympathetic supply: comes from sphenopalatine ganglion.
 - 3- Sensory nerve supply: sensory nerves have their cell bodies in trigeminal ganglion

Cerebrospinal fluid

1- Site:

It fills the ventricles of the brain (lateral ventricles, 3rd ventricle & 4th ventricle & subarachnoid space (the space between the arachnoid mater & pia mater around the brain).

2- Volume:

About 150 ml

3- Formation of CSF:

- a) 70 % is formed by the choroid plexus (capillaries covered by epithelial cells connected together by tight junctions)
- b) 30 % is formed around cerebral vessels & from ventricular walls.

4- Rate of production of CSF:

550 ml/ day i.e. the CSF turns over 3.7 times per day

5- Circulation of CSF:

CSF flows from the lateral ventricles to the 3rd ventricle then to the 4th ventricle then to the subarachnoid space around the brain

6- Absorption of CSF:

It occurs via the arachnoid villi (projections from the arachnoid mater that protrude into the venous sinuses) which allow CSF to leave the subarachnoid space & reach the blood.

Absorption takes place largely by bulk flow.

7- CSF pressure:

7- 18 cm H₂O

Elevation of CSF pressure does not affect the rate of CSF formation.

However, it increases its absorption.

Absorption stops completely if pressure drops below 7 cm H₂O

8- Composition of CSF:

Compared to plasma, CSF has:

- The same osmolarity & same concentration of Na⁺ & HCO₃⁻
- Higher concentration of Mg⁺⁺, Cl⁻ & creatinine
- Lower concentration of proteins, glucose, K⁺, Ca⁺⁺, inorganic phosphates, urea, uric acid, lactic acid & cholesterol

The composition of CSF is similar to that of brain interstitial fluid.

9- Functions of CSF:**A) Protective function of CSF:**

The brain is supported within the arachnoid by:

- a- Water bath of CSF:
CSF acts as a cushion that absorbs a blow to the head & lessens its impact on the brain.
 - b- Blood vessels & nerve roots
 - c- Fine fibrous arachnoid trabeculae
- The brain is immersed in CSF
The net weight of the brain is reduced from 1400 gm to 50 gm.
The reduction of weight increases the efficiency of the previous 3 mechanisms in protecting the brain against head trauma
- B) CSF acts as a medium delivers substances (e.g. nutrients, neurotransmitters & drugs) from one area of the brain to another.
 - C) CSF acts as a sink that receives waste products of brain metabolism & delivers them to venous blood

Blood- brain barrier (BBB)

- Definition:

BBB is the barrier that limits movement of substances from capillary blood to brain tissues & CSF

- BBB is due to the presence of tight junctions between:

- a) Capillary endothelial cells in the brain
- b) Epithelial cells of the choroid plexus

- However, movement of substances in the opposite direction i.e. from the brain & CSF to blood is more free due to the presence of:

- a) Bulk flow of CSF across arachnoid villi
- b) Active transport mechanisms that move substances from the brain to blood

- Movement of substances across BBB:

Movement is directly proportional to lipid solubility but is inversely proportional to molecular size e.g.:

- a) H₂O, CO₂ & O₂ can rapidly cross the barrier, while H⁺ & HCO₃⁻ cross it slowly. This has physiologic significance in control of respiration.
- b) Glucose (Which is the main source of energy for nerve cells) crosses BBB easily due to the presence of special glucose transporter in the wall of cerebral capillaries
- c) Movement of proteins & protein- bound substances across the barrier is very limited

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- Development of the BBB:

BBB effectively develops in the first few years of life.

That is why in severely jaundiced infants, but not in adults, bilirubin can reach the brain tissue & cause damage to certain areas in the brain (kernicterus)

kernicterus

- Functions of BBB:

- 1- Maintains the environment of the brain constant since neurons in the brain are very sensitive to changes in ionic composition in brain interstitial fluid
- 2- Protects the brain from lipid- insoluble toxins in blood
- 3- Prevents the escape of neurotransmitters to blood.

- Circumventricular organs:

These are 4 small areas around the brain stem that have fenestrated capillaries i.e. no BBB in these organs.

These areas are described as being outside the BBB

The BBB is not present in these areas because the function of these areas requires free movement of substances across the capillaries.

The Circumventricular organs are:

- 1- The posterior pituitary gland & part of the median eminence of the hypothalamus:

These areas secrete hormones directly into blood

- 2- Area postrema:

This is a chemoreceptor zone that is stimulated by chemical changes in blood & causes vomiting

- 3- The subfornical organ:

This area is stimulated by angiotensin II in blood leading to thirst & increased water intake

- 4- Organum vasculosum of the lamina terminalis (OVLT):

This is the site of osmoreceptors controlling vasopressin secretion.

In addition to the previous 4 areas, BBB can be disrupted when there is sudden marked elevation of arterial blood pressure or in parts of the brain where there is infection, injury or tumors.

kernicterus

A →

Cerebral blood flow

Measurement of cerebral blood flow:

1- Kety method:

- This method applies the Fick principle:

$$\text{Flow} = \frac{\text{Amount of substance taken by organ (Qx)}}{\text{Arterial (Ax) - venous (Vx) concentration of substance}}$$

i.e. Cerebral blood flow (CBF) = $Qx / Ax - Vx$

- The substance used is inhaled nitrous oxide (N_2O)
- The normal cerebral blood flow in young adult is 55 ml/ 100 g/ minute.

The flow for the whole brain = 750 ml/ minute

- Kety method measures flow to all perfused parts of the brain.

It gives no information about regional differences in blood flow.

The following methods are used to detect regional cerebral blood flow:

2- Positron emission tomography (PET):

Blood flow is closely linked to their metabolic activity.

So, 2- deoxyglucose is labeled with positron emitter & is injected in blood.

Using special group of detectors placed on the scalp, the distribution of labeled 2- deoxyglucose in different brain areas can be detected.

This distribution is proportional to regional blood flow.

3- Functional magnetic resonance imaging (fMRI):

Magnetic resonance imaging depends on detection of resonant magnetic signals from different tissues.

Oxyhaemoglobin & Deoxyhaemoglobin produce different resonance signals.

This gives an index of regional blood flow.

Using PEM & fMRI, the average blood flow:

- a) In gray matter was found to be 69 ml/ 100 gm/ minute
- b) Compared to 28 ml/ 100 gm/ minute in white matter.

Regulation of cerebral circulation:

The brain receives about 15 % of the COP

Brain consumes 20 % of total O₂ consumption of the body.

There is marked fluctuations in blood flow in different brain areas.

However, the cerebral circulation is regulated, so that the total blood flow remains remarkably constant.

Factors involved in regulation of cerebral blood flow:1- Metabolic regulation (Most important):

CBF is adjusted to metabolic demands of the brain.

Different vasodilator mediators increase CBF in areas of high metabolic activity e.g. H^+ , CO_2 , K^+ & nitric oxide

2- Effect of arterial PCO_2 :

CO_2 (strong vasodilator) is a major determinant of CBF.

CBF increases linearly when arterial PCO_2 increases from 20- 80 mmHg

Mechanism:

$++$ Arterial $PCO_2 \rightarrow ++ H^+$ concentration in brain interstitial fluid.

High H^+ & nitric oxide $\rightarrow$ $----$ intracellular Ca^{++} in vascular smooth muscles of cerebral vessels $\rightarrow$ VD

3- Autoregulation:

It is the ability of the brain to maintain total CBF nearly constant despite large changes in perfusion pressure (ABP between 65- 140 mmHg).

Mechanism:

Myogenic and/ or metabolic

4- Effect of arterial PO_2 :

Moderate changes in arterial PO_2 do not significantly affect CBF.

Marked hypoxia i.e. PaO_2 drops below 50 mmHg $\rightarrow ++$ CBF.

Hypoxia releases adenosine $\rightarrow$ cerebral VD

5- Neural regulation (autogenic & sensory nerves):

It plays limited role in regulation of CBF.

However, $++$ ABP $\rightarrow ++$ sympathetic VC discharge to cerebral vessels $\rightarrow$ constant CBF (autoregulation)

6- Role of intracranial pressure (ICP):

- Rise of intracranial pressure e.g. cerebral hge compresses cerebral vessels & $---$ CBF

This initiates Cushing reflex i.e. $++$ ABP & $---$ HR

$++$ ABP maintains constant CBF with $++$ ICP.

However, if ICP is markedly elevated, the $++$ ABP will not be enough to maintain CBF & brain ischemia occurs

- Rise of cerebral venous pressure causes immediate rise of ICP & decreases cerebral blood flow & vice versa.

- During exposure of the body to upward acceleration, blood moves to lower part of the body.

Arterial pressure at the level of the head ---- → --- CBF → cerebral ischemia
→ blackening out phenomenon & loss of consciousness

Compensatory mechanisms:

Both venous pressure & ICP falls → the pressure on the cerebral vessels decreases & CBF is not much affected by the --- ABP

- During exposure of the body to downward acceleration, blood moves to upper part of the body.

Arterial pressure at the level of the head increases → ++ CBF, reddening phenomenon & cerebral vessels may rupture.

Compensatory mechanisms:

Both venous pressure & ICP increases → the pressure on the cerebral vessels increases & protects them from rupture due to rise of arterial pressure

Cutaneous circulation

Organization of cutaneous circulation:

2 types of vessels are present in the skin:

1- Nutritive vessels:

These are ordinary arterioles, capillaries & veins

2- Vascular structures concerned with heat regulation, they include:

a) Subcutaneous venous plexus:

They can hold large quantities of blood (to heat the surface of the skin)

b) Arterio- venous anastomosis:

They are large direct communications between arterioles & venous plexuses
Arterio- venous anastomoses are present in the palm of the hands, sole of feet, the lips, the nose & the ear.

They have strong muscular coats innervated by sympathetic adrenergic vasoconstrictor nerves.

In cold, they constrict → ---- blood flow to the subcutaneous venous plexus
→ minimal heat loss & vice versa.

The counter current heat exchange mechanism:

Warm blood entering the extremities via arteries gives up some of its heat to cold blood in adjacent vein, returning from the extremities.

Result:

a) Cool blood perfusing the peripheral areas of the body

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b) Blood re- entering the core of the body is warmer than it would otherwise be.

Regulation of cutaneous circulation:

1- Effect of sympathetic innervation:

- Sympathetic adrenergic fibers → VC of skin arterioles
- Sympathetic cholinergic fibers → VD & ++ secretion of sweat glands via release of kinins

So, in intense sympathetic stimulation e.g. hge, skin is pale & cold (due to VC) & clammy (sweat secretion)

2- Effect of environmental & body temperature:

- If ++, Thermoreceptors in skin and/ or hypothalamus are stimulated. This initiates reflex dilatation of cutaneous vessels to help the body to get rid of excess heat or to minimize heat gain
- If ----, a reflex is initiated from Thermoreceptors → VC to minimize heat loss.

However, if skin temperature is very low, cutaneous vessels dilate due to blocking of nerve impulses & relaxation of smooth muscles. This prevents freezing of tissue

- Direct application of heat to an area of skin → VD & vice versa. These effects are independent of temperature changes of the blood.

They also occur in denervated skin i.e. not reflex in origin

- During muscular exercise, body temperature rises & skin vessels dilates in spite of increased sympathetic activity which accompany muscular exercise

3- Response to mechanical stimuli:

- White reaction (line)
- Triple response (See capillary circulation)

GOOD LUCK